# What Is Hot and New in Basic and Translational Science in Liver Transplantation in 2020–2021?—Report of the Basic and Translational Research Committee of the International Liver Transplantation Society

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## INTRODUCTION

The 2020 Joint Annual Congress of the International Liver Transplantation Society (ILTS), European Liver and Intestine Transplant Association (ELITA), and Liver Intensive Care Group of Europe (LICAGE) was supposed to be held in Istanbul, Turkey, in May 2020. Because of the coronavirus disease 2019 (COVID-19) pandemic, the physical conference was transformed into a virtual congress held between May 5 and 8, 2021. This fully online event was attended by 1098 delegates from 66 countries (Figure 1). A total of 730 abstracts were presented during the meeting. The impact of basic and translational research at the ILTS meetings remains stable over the years with ~8% of the total abstract volume (Table 1).

Members of the ILTS Basic and Translational Research Committee attended all sessions of the meeting to select the most novel, innovative, and promising studies in the field of basic and translational science. Here, we present an overview of "what is hot and new in 2020–2021" categorized in 6 main themes (Figure 2), including (1) transplant oncology and tumor biology, (2) novel biomarkers, (3) ischemia-reperfusion injury (IRI) and organ preservation, (4) mechanism of disease and injury, (5) liver immunobiology and tolerance, and (6) COVID-19. Most abstracts fell within themes 1–3. In the included abstracts, a variety of state-of-the-art laboratory techniques was used in these studies. In the included abstracts, a variety of state-of-the-art laboratory techniques, such as next-generation molecular assays, multiomics approaches, and bioinformatics, was used.

### Transplant Oncology and Tumor Biology

The biology of liver tumors related to liver transplantation (LT) remained to be one of the largest categories among the presented abstracts at the ILTS virtual congress. Understanding the mechanisms of posttransplant tumor recurrence has major clinical significance in the treatment

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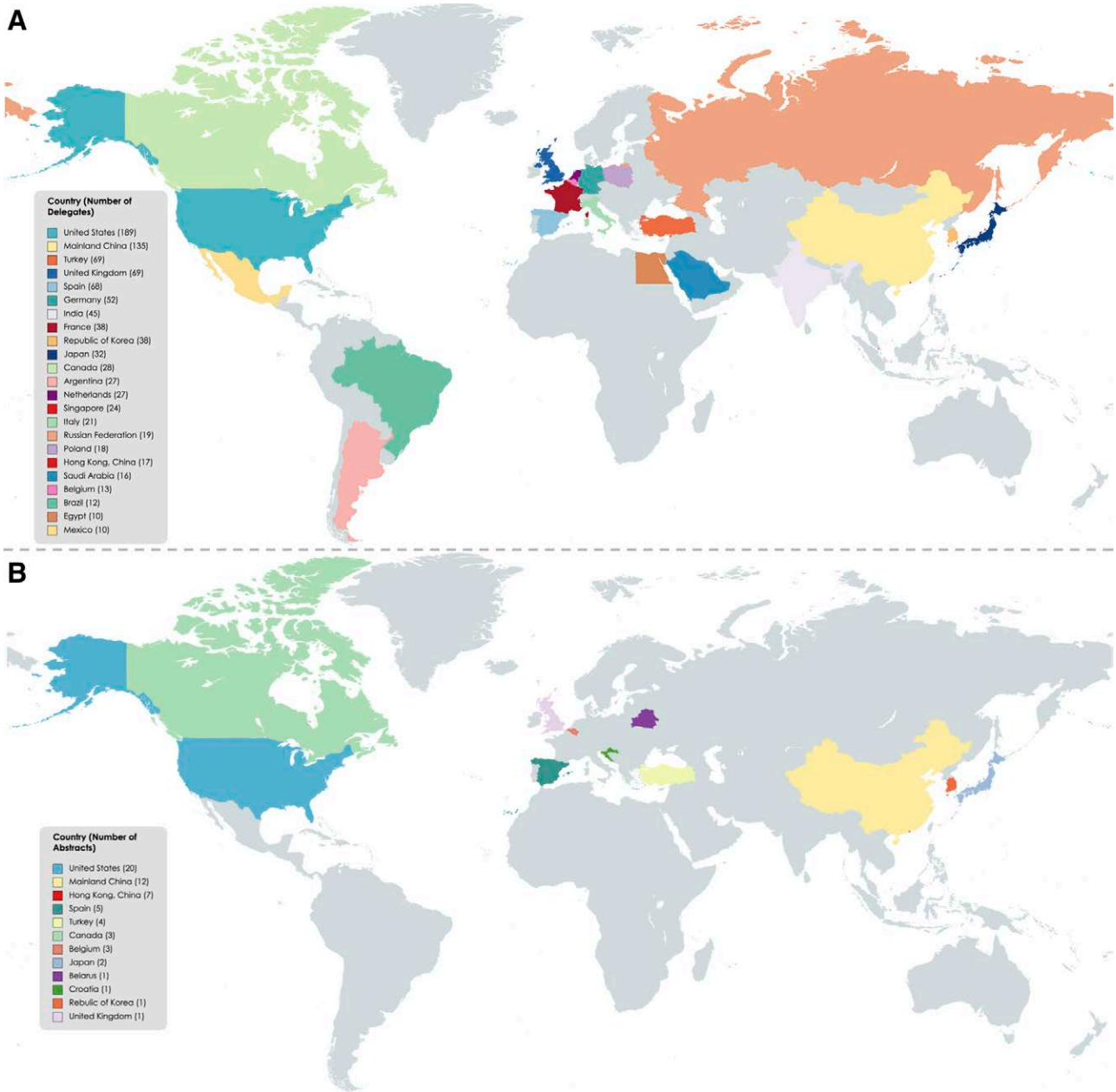


**FIGURE 1.** Countries with (A) ≥10 delegates and (B) the presenting authors of basic and translational science abstracts at the 2020–2021 Joint ILTS-ELITA-LICAGE Meeting. This figure was regenerated with permission of the ILTS. ELITA, European Liver and Intestine Transplantation Association; ILTS, International Liver Transplant Society; LICAGE, Liver Intensive Care Group of Europe.

**TABLE 1.**

**Absolute and relative frequencies of basic and translational science-related abstracts presented at the Joint ILTS-ELITA-LICAGE Meetings in 2017–2021**

| Year/venue | Countries represented (no.) | Total abstracts (no.) | Late-breaking abstracts (no.) | Basic and translational research abstracts (no.) | Basic and translational research abstracts (%) |
|---|---|---|---|---|---|
| 2017/Prague | 61 | 860 | 65 | 70 | 8.1 |
| 2018/Lisbon | 58 | 759 | 112 | 72 | 9.5 |
| 2019/Toronto | 52 | 900 | 74 | 75 | 8.3 |
| 2020–2021/virtual[a] | 66 | 730 | 89 | 60 | 8.2 |

[a] Due to the COVID-19 pandemic, the 2020 ILTS Congress in Istanbul was postponed and held in a fully virtual setting in 2021.
COVID-19, coronavirus disease 2019; ELITA, European Liver and Intestine Transplantation Association; ILTS, International Liver Transplantation Society; LICAGE, Liver Intensive Care Group of Europe.

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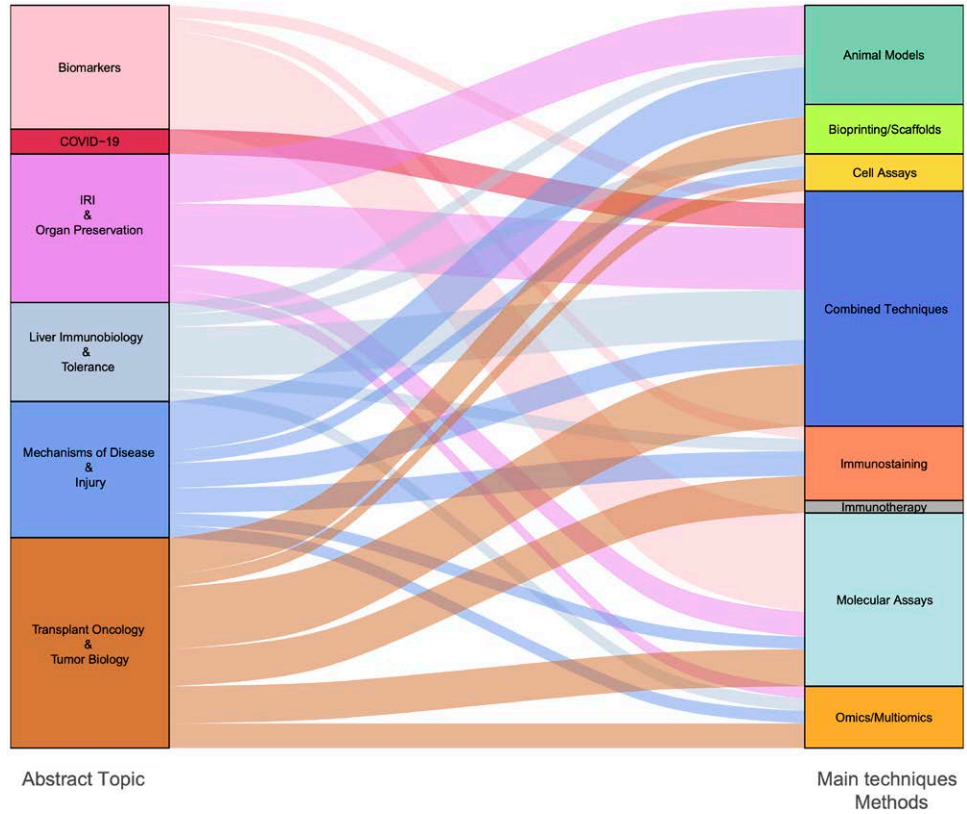


**FIGURE 2.** Sankey diagram depicting distribution of the topics and main techniques used in the 60 basic science studies presented at the 2020–2021 Joint ILTS-ELITA-LICAGE Meeting. Each (total n = 60) abstract has been classified into one of the 6 topics/themes and based on the main technique and methodical approach used. COVID-19, coronavirus disease 2019; ELITA, European Liver and Intestine Transplantation Association; ILTS, International Liver Transplant Society; IRI, ischemia-reperfusion injury; LICAGE, Liver Intensive Care Group of Europe.

of hepatocellular carcinoma (HCC). In a plenary oral presentation, Chakravarthy et al have reported their findings on the clonal evolution of recurrent HCC in the context of the posttransplant immune environment.[1] For this, the authors examined tissue samples from recurrent HCCs in immunocompromised transplant recipients and from immunocompetent patients following partial hepatectomy and compared these with samples from the primary tumor. After performing methylome and whole-exome sequencing, they observed a highly heterogeneous epigenetic evolution in the posttransplant HCC recurrences, where the natural immune reaction was reduced with the use of immunosuppression. Most of the differentially methylated genes in the immunosuppressed versus immunocompetent cohort were involved in the cell cycle. Therefore, they postulated that these novel findings could facilitate the identification of future targets for chemopreventive agents.

Using samples from HCC patients and a murine animal model, Wang et al aimed to explore the role of myeloid-derived suppressor cells (MDSCs) in tumor recurrence. The MDSCs are pathologically activated neutrophils and monocytes with potent immunosuppressive activity that could serve as potential targets in various oncological and autoimmune diseases.[2] This study suggests that CXCL1/CXCL2 signaling is responsible for MDSCs mobilization, further promoting HCC recurrence.[3] Tolerogenic immune cell populations may play a role not only in HCC recurrence but also in response to primary treatment. In a further study, Nunez et al[4] have performed flow cytometry on clinical blood samples from HCC patients on the waiting list showing an association between lymphopenia and the parallel increase of MDSCs, regulatory T cells, and failure to respond to transarterial chemoembolization.[4] In a study from the same group, the otherwise poorly understood role of C3a complement in HCC was explored. First, they showed that increased plasma C3a is strongly associated with the extent of hypoxic/ischemic allograft injury following LT. Second, patients with tumor recurrence and shortened recurrence-free survival expressed higher levels of C3a. This was confirmed in a functional setting showing that HCC cell lines with metastatic potentials also expressed higher C3a receptors and significantly upregulated metastasis-related genes in response to C3a treatment.[5]

Adenosine is a well-known regulator of hypoxia/ischemia related innate and adaptive immunological responses. Pang et al[6] determined that adenosine and A1-receptor signaling lead to the recruitment of activated plasmacytoid dendritic cells, which subsequently promote posttransplant HCC recurrence via an enhanced differentiation of naive T cells into regulatory T cells in vitro.

Further reports have investigated the immune regulatory background and mechanisms of HCC and cholangiocarcinoma tumor genesis and recurrence using state-of-the-art techniques and in vitro and in vivo models.[7-11] The use of bioprinting in cancer research holds promise to better mimic the complex microenvironment of hepatobiliary malignancies and has potential to move research from the

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traditional planar cell cultures to models that are biologically more relevant.[12] Several talks at the ILTS 2020–2021 meeting focused on the introduction, feasibility, and cost efficiency of 3-dimensional bioprinted models to mimic the microenvironment of HCC, cholangiocarcinoma, and colorectal liver metastases.[13-15]

In summary, the current research in transplant oncology and tumor biology focuses predominantly on the characterization of the tumor microenvironment and immune responses, especially in post-LT tumor recurrence.

## Novel Biomarkers

LT is a complex and major surgical procedure triggering a wide range of physiological responses and subcellular pathways. With the persistent organ shortage, accurate prediction of graft and patient outcomes is of crucial clinical importance to ensure optimal use of allografts.

The data from INTERLIVER study demonstrated the role of microarray-based gene expression analysis in advanced molecular diagnostics in LT, introducing the concept of a "molecular microscope diagnostic system." The INTERLIVER study is a large-scale prospective observational multicenter study aiming to improve the traditional semiquantitative histological evaluation and investigate the relationship of molecular phenotypes in LT biopsies in context of the histological phenotypes and the clinical features and outcomes (NCT03193151). Madill-Thomsen et al[16] presented the INTERLIVER data on molecular injury phenotypes in human LT describing novel molecular characteristics for steatohepatitis and fibrosis/cirrhosis. In another talk based on the same study, the authors demonstrated an association of molecular microscope diagnostic system phenotypes with histological rejection in a large cohort of 235 liver biopsies.[17] These findings suggest that unsupervised and semiautomatic molecular phenotyping and machine learning may play an important role in the near future by improving accuracy and precision of molecular diagnostics in the clinical setting.

Besides the above-described multicenter study, further innovative reports focused on prognostic tissue biomarkers. Posttransplant allograft fibrosis/cirrhosis is a relatively uncommon but serious long-term complication often leading to graft loss and re-LT. Although most cases can be attributed to recurrent disease, such as hepatitis C and autoimmune liver diseases, little is known about the underlying mechanisms and risk factors of allograft fibrosis without evidence of recurrent liver disease.[18] Wang et al analyzed a set of 23 single-nucleotide polymorphisms, which were associated with liver fibrosis using 232 liver allograft samples. They were able to identify 4 donor single-nucleotide polymorphisms (rs430397, rs1695, rs12304647, and rs1800630) associated with graft fibrosis, suggesting that the inclusion of donor gene polymorphisms in prognostic models may serve as a potential clinical instrument for the prediction of post-LT allograft fibrosis. These findings are in line with previous reports on the key contribution of genetic susceptibility to clinical outcomes in chronic liver disease and LT.[19,20]

In contrast to most tissue-based biomarkers, circulatory markers may serve as simple, less-invasive, and real-time screening tools. Exosomes are small endosomal-derived microvesicles, receiving an increased scientific interest over the past decades.[21] Because of their regulated formation and cell-targeting specificity, they could serve not only as noninvasive diagnostic biomarkers but also as potential therapeutic nanocarriers.[22,23] Qiu et al analyzed the association of exosomal micro ribonucleic acids (microRNAs) with viral hepatitis B virus (HBV) reactivation after LT. In a pilot cohort of patients with and without HBV reactivation, they identified exosomal microRNA-766 as a promising prognostic biomarker and a potential functional target for the treatment of HBV reactivation.[23,24]

Further exploring the role of novel, innovative circulatory biomarkers, Izzy et al determined that symmetric dimethylarginine, as a marker of endothelial injury, may predict future renal failure in LT recipients.[25] Glycomic signatures, a comprehensive analysis of glycans in a specific biological setting, is an emerging tool in the identification of prognostic biomarkers. A prospective study from Belgium analyzed the serum glycomic signatures of 117 LT patients. In this cohort, graft loss at 3 mo was associated with increased undergalactosylation (a marker of inflammation) and an increased presence of fucosylated and triantennary glycans, which are both signs of liver regeneration. The multivariable logistic regression analysis showed a strongly significant association of graft loss and altered glycomics signature. Such markers may assist in the difficult clinical decision making with respect to early re-LT.[26]

Achievement of operational tolerance and long-term stability without immunosuppression would be ideal in solid organ transplantation to avoid the consequences of sustained exposure to immunosuppression. Circulating small RNAs were among the main targets of biomarker research for many years. Kuscu et al reported a decrease of transfer RNA fragments in tolerant patients (17 tolerants out of 55 pediatric LT patient samples), whereas the proportion of YRNA fragments was increased. Distribution of small RNA species in healthy subjects was similar to that observed in the tolerant group. Based on these findings, lower levels of transfer RNA fragments and higher levels of YRNA fragments may result in lower levels of immune activity in tolerant patients.[27]

Recent improvements in biomarker discovery, molecular diagnostics, multiomics, extracellular vesicle research, and liquid biopsy approaches hold promise for an improved depiction of complex biological responses. Current research in the field of biomarkers in LT is focusing on various molecular or genetic tissue signatures and circulatory markers to better characterize and predict clinical outcomes post-LT.

## IRI and Organ Preservation

Warm and cold ex situ machine perfusion and ischemia-free LT continue to be a strong focus of preservation injury research.[28] In a study with discarded human livers, it was shown that fibrinogen levels increased during normothermic machine perfusion, which was associated with higher rouleaux formation of erythrocytes more vascular plugging, and consequently, increased vascular resistance.[29] In an attempt to improve the preservation solution used for hypothermic machine perfusion, the effect of different oncotic agents was investigated in rodent models. Beneficial effects for solutions containing polyethylene glycol 35 as an oncotic agent (eg, Institute George Lopez) compared with solutions containing hydroxyethyl starch

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(eg, University of Wisconsin) were observed with better mitochondrial protection,[30] reduced oxidative stress, and less inflammatory response.[31]

A novel technique to improve mitochondrial function was investigated by Bajwa et al.[32] The authors intravenously administered mitochondria isolated from healthy mouse livers to living mice 1 d before LT. Hepatocellular uptake of mitochondria was demonstrated and it was associated with higher adenosine triphosphate levels, higher oxygen consumption, improved histology, and higher levels of energy metabolism-enhancing genes (Pgc1a and Ppar).

More recently, gene silencing through either RNA interference or clustered regularly interspaced short palindromic repeats–associated protein 9 technology has gained interest in the field of organ transplantation.[33,34] Small interfering RNA delivered during hypothermic machine perfusion of rat livers effectively inhibited gene expression of apoptosis-associated gene fetal alcohol syndrome in rat livers with decreased apoptosis, inflammation, and IRI.[33] Identification of novel gene targets inducing liver IRI could be performed with clustered regularly interspaced short palindromic repeats–based library screening[34] or by using single-cell RNA sequencing.[35] Wang et al[35] collected tissue of donor livers at different time points during preservation and then performed single-cell sequencing. This way, they were able to describe the atlas of intrahepatic cells during LT and their expression profiles after IRI, which may help to identify novel therapeutic targets in the future. One of the main observations was the upregulation of the plasminogen activator urokinase receptor gene after reperfusion (plasminogen activator urokinase receptor) that was mainly concentrated in vascular cell adhesion molecule-1$^{low}$ endothelial cells and tumor necrosis factor$^{+}$ macrophages, indicating that it may play an important role in recruiting monocytes and promoting leukocyte–endothelial cell interaction.[36]

Immune cells, including neutrophils and natural killer (NK) cells, are known as main amplifier of hepatic IRI.[37-39] Cheng et al[38] quantified gene expression profiles of novel infiltrated immature neutrophils (cluster of differentiation [CD]66b$^{+}$, CD10$^{-}$) in 31 human liver allograft biopsies taken 2 h after portal vein reperfusion. Quantitative PCR and flow cytometry data showed that CD10$^{-}$ was downregulated after reperfusion, and CD10$^{-}$ levels were reversely correlated with postoperative liver enzymes and total bilirubin. Neutrophil marker CD66b$^{+}$ and HLA-DR mRNA levels were elevated after reperfusion and correlated with each other. This study indicates a novel immunostimulatory role of immature neutrophils in promoting posttransplant graft injury, which could be a target for future therapies. Yang et al[39] retrospectively assessed 110 patients on dynamic change of peripheral immune cells before and 2–4 d after LT. Peripheral immune cell profiling revealed a depletion of NK cells after LT, which was more prominent in patients with early allograft dysfunction compared with those with immediate graft function. These results were substantiated in a mouse model showing recruitment of NK cells to the liver after reperfusion. Specific depletion of NK cells through anti-Asialo GM1 antibody attenuated IRI, which could also represent a novel therapeutic strategy.

In summary, recent developments in IRI and organ preservation research resulted in further refinement of machine perfusion techniques and both identified and exploited novel therapeutic targets in the complex pathophysiology of IRI.

## Mechanisms of Disease and Injury

Researchers from the United States aimed to further elucidate the pathophysiology of alcoholic liver disease. Using a murine model, it was demonstrated that hepatic mitochondrial depolarization and subsequent type 2 mitophagy after ethanol are driven by acetyl aldehyde formation.[40] Two studies by Ozdemir et al[41,42] investigated hypercholesterolemia-induced liver injury. In one study, 70 biopsies of LT recipients were analyzed and they found that high serum cholesterol levels were associated with apoptosis and activation of hepatic stellate cells, inducing inflammation, fibrosis, and oxidative stress, leading to progression of allograft injury.[41] In another study by the same group, they showed that hepatocyte growth factor (HGF) is critical for organ protection and liver regeneration in LT patients with hypercholesterolemia via its angiogenetic and antiapoptotic effects.[42] A further report from the Ankara group found an important role for HGF in hepatocyte proliferation (Ki-67) after transplantation of partial liver grafts from living donors.[43] For this study, posttransplant biopsies of 62 patients were scored for inflammation and fibrosis and analyzed for the development of liver failure 18 mo after the initial biopsy. Higher expression of HGF on immunohistochemistry was associated with increased angiogenesis (studied with CD31) and hepatocyte proliferation (studied with Ki-67). The development of liver failure decreased with increasing expression of HGF. In this light, HGF-based drugs could be further explored to suppress allograft failure because of incomplete liver regeneration, such as in small-for-size living donor liver allografts. Liu et al[44] found that increased signaling of the glycoprotein amphiregulin after partial mice LT promotes mitochondrial biogenesis and regeneration. After implantation, amphiregulin expression increased markedly in split liver grafts but not in full-size grafts. Suppressed amphiregulin signaling and subsequent inhibition of mitochondrial biogenesis may partly be responsible for poor outcomes of small-for-size grafts.

On another note, microbiota in bile may be involved in the pathogenesis of biliary complications. Bile of patients with biliary complications after LT was found to be enriched with *Proteobacteria* and *Staphylococcus*.[45]

In summary, results from studies animal models as well as immunohistochemistry analysis of human biopsies add to our understanding of the mechanisms of alcoholic liver disease, hypercholesterolemia-induced liver injury, and liver regeneration.

## Liver Immunobiology and Tolerance

Rejection remains an important cause of graft loss after LT and several research groups investigated mechanisms of liver tolerance.[46-50] Emamaullee et al[47] developed a liver-specific imaging mass cytometry panel and an informatics-based analysis pipeline to quantify which lymphocytes are involved in chronic rejection. Using this technique, few CD3$^{+}$ and CD8$^{+}$ effector T cells were identified in biopsies of livers undergoing re-LT because of chronic rejection,

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but more CD68+ macrophages. Additionally, heterogenous lymphocyte subsets were present in livers with chronic rejection compared with controls. This technique may provide quantitative information regarding lymphocyte subsets to better understand graft rejection and search for novel therapeutic targets.

Korotkov et al[48] treated 10 patients with portal venous infusion of mesenchymal stem cells (MSCs) during allograft reperfusion as an induction immunosuppression. Two patients developed mild acute cellular rejection and there were no adverse events of MSC therapy. All patients were switched to 3-component immunosuppression with tacrolimus, mycophenolate mofetil, and steroids. Considering patients are still on triple therapy, no conclusion can yet be drawn from additional MSC therapy. A prospective controlled trial is needed to confirm superiority of this approach compared with standard immunosuppressive regimens. Pierre et al[49] investigated the association between tolerance and the plasma microbiome of 55 patients after LT. Patients with operational tolerance (no immunosuppression) displayed the highest levels of alpha diversity compared with patients on maintenance immunosuppression (tacrolimus) and weaning immunosuppression (monitored tacrolimus withdrawal). *Candida albicans*, *Flavobacterium*, and *Phialophora* were scarce in patients with operational tolerance, but there was greater abundance of *Cystofilobasidium*, *Helicogloea*, and *Sebacina*. The same group evaluated stool samples of 21 patients with recurrent nonalcoholic fatty liver disease and found significant loss of *Akkermansia* and *Firmicutes* and increased *Fusobacterium* and *Bacteroidetes*.[50]

Novel immunological approaches seek to overcome common problems in LT, such as cytomegalovirus (CMV) after LT. Researchers from Spain showed that quantification of CMV-specific polyfunctional T-cell responses with intracellular cytokine staining could be a specific marker to identify patients who achieve spontaneous CMV control.[51]

To conclude, novel diagnostic and quantitative measures for graft tolerance are investigated to ultimately find targets for therapeutic therapies.

### Coronavirus Disease 2019

Two studies on COVID-19 and its impact on LT outcomes were presented. In a multicenter study from Spain, the persistence of antinucleocapsid immunoglobulin G antibodies in 71 LT recipients 6 mo after COVID-19 resolution was evaluated. Recipients of LT exhibited a lower incidence of antinucleocapsid immunoglobulin G antibodies compared with immunocompetent controls (62 versus 62).[52] Lovatt et al[53] report successful re-LT in 3 patients previously infected with COVID-19. Despite being clinically immunosuppressed, all patients demonstrated competent CD4+ T-cell responses against COVID-19 after infection and after the first vaccine.

## DISCUSSION

High quality of basic and translational research was presented at the 2020–2021 joint ILTS-ELITA-LICAGE meeting, despite the multiple clinical, technical, and potentially life-threatening challenges, which have arisen from the global COVID-19 pandemic. The future of LT research was presented within 6 thematic areas during the conference. With advanced laboratory techniques, a better understanding of liver tumor biology is being revealed, which provides potential targets for novel therapies. As transplant oncology continues to evolve as a promising clinical field in LT and cancer management, more landmark studies are expected and will be encouraged in future ILTS meetings. Developments in biomarker discovery have identified numerous novel targets and prognostic tools to predict outcome after LT, which may aid in clinical decision making and better donor–recipient matching. Ongoing scientific efforts are aimed at optimizing organ preservation, mainly by the introduction of various ex vivo machine perfusion technologies. Graft modification via application of allograft therapies during machine perfusion before transplantation is likely to emerge as a major rehabilitative and assessment intervention in the coming years. In addition, methods to induce tolerance and reduce rejection after transplantation show promise in experimental models and may be translated to clinical application as research advances. In summary, the virtual platform of the 2020–2021 joint ILTS-ELITA-LICAGE congress provided an interactive environment for researchers to share their experiences and studies. Future hybrid events, face-to-face and virtual, will be essential for greater dissemination of research advances in the field of LT.

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